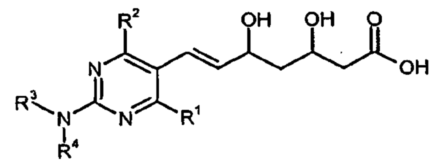
PROCESS AND INTERMEDIATE COMPOUNDS USEFUL IN THE PREPARATION OF STATINS, PARTICULARLY ROSUVASTATIN

The present invention concerns a process and intermediate compounds useful in the preparation of statins, particularly Rosuvastatin.

According to the present invention, there is provided a process for the preparation of a compound of formula (7):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

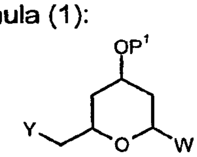
R^2 represents an aryl group, preferably a 4-fluorophenyl group;

R^3 represents hydrogen, a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and

R^4 represents hydrogen, a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

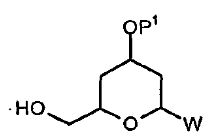
which comprises

a) hydroxylating a compound of formula (1):

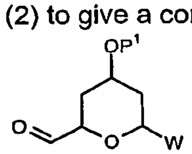


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

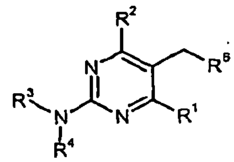
to give a compound of formula (2):



b) oxidising the compound of formula (2) to give a compound of formula (3):

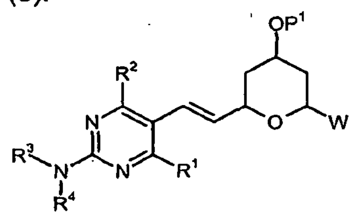


c) coupling the compound of formula (3) with a compound of formula (4):



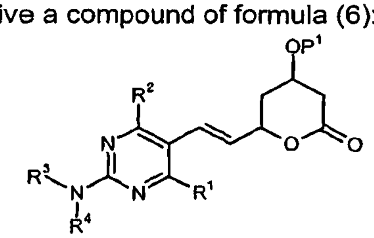
wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,

to give a compound of formula (5):



wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

d) when W represents $-OP^2$, removing any P^2 protecting group and oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, removal of any P^1 protecting groups, and optionally removing any additional protecting groups to give a compound of formula (7).

In step (e), any P^1 protecting groups and any additional protecting groups may be removed individually or together and prior to ring opening, during ring opening or after ring opening of the compounds of formula (5) or (6).

Preferably, in steps (a) to (c), W is OP^2 for the compounds of formula (1), (2), (3) and (5).

Protecting groups which may be represented by P^1 and P^2 include alcohol protecting groups, examples of which are well known in the art. Particular examples

include tetrahydropyranyl, benzyl and methyl groups, and optionally substituted variants thereof. Substituents may advantageously be used to modify the ease of introduction or removal of the protecting group. Preferred protecting groups are silyl groups, for example triaryl- and especially trialkylsilyl groups. Especially preferred examples are trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl groups.

Protecting groups which may be represented by P^1 and P^2 may be the same or different. When the protecting groups P^1 and P^2 are different, advantageously this may allow for the selective removal of only P^1 or P^2. Preferably, when the protecting groups P^1 and P^2 are different, P^1 is a tetrahydropyranyl, benzyl, or silyl group and P^2 is a methyl group. More preferably, when the protecting groups P^1 and P^2 are different, P^1 is a benzyl, or silyl group and P^2 is a methyl group.

Protecting groups which may be represented by R^3 and R^4 include amine protecting groups, examples of which are well known in the art. Particular examples include benzyl groups, carbamates (such as CBZ, Boc, Fmoc), phosphate, thiophosphate, silyl groups and, when R^3 and R^4 together are a single protecting group, an imine group.

Hyrdoxylation of compounds of formula (1) can be achieved by methods known in the art for displacing a halo group with a hydroxide source. Preferably, the process comprises contacting the compound of formula (1) with a source of hydroxide. Hydroxide sources include hydroxide salts, especially ammonium or alkali metal hydroxides, particularly lithium, sodium or potassium hydroxide, and various aqueous media such as water in the presence of basic media such as N-methylpryrrolidinone, HMPA, Al_2O_3, $CaCO_3$, Na_2CO_3, K_2CO_3 or KO_2/18-crown-6, silver salts such as $AgNO_3$ or Ag_2O, or oxidants such perbenzioc acid. A particularly preferred process comprises contacting the compound of formula (1) with 5 molar equivalents of KOH in the presence of dimethylsulfoxide solvent at a temperature of, for example, about 50°C.

Alternatively, hydroxylation may be achieved by first displacing the halogen with a leaving group such as acetate, triflate or sulphate optionally in the presence of a silver salt, then displacing the leaving group with a hydroxide source. A particularly preferred process comprises contacting the compound of formula (1) with 3 molar equivalents of NaOAc in the presence of dimethylformamide solvent and tetra-n-butylammonium chloride at a temperature of, for example, about 100°C, isolating the acetyl compound and contacting with potassium carbonate in the presence of methanol solvent and at a temperature of, for example, about 0°C.

Oxidation of compounds of formula (2) can be achieved using oxidation systems known in the art for the oxidation of alcohols, especially those known in the art for the oxidation of primary alcohols. Examples include oxidation with Dess-Martin periodinane, bromine, Swern oxidation or various metal based oxidations such as Fetizon reagent, manganate based reagents, and chromate based reagents such as Collins reagent. Swern oxidation is preferred. When Swern oxidation is employed, preferred conditions

comprise the use of dimethyl sulphoxide and oxalyl chloride or bromine in a solvent such as dichloromethane or dichlormethane/THF mixtures, at reduced temperature, such as from 0 to -100°C, preferably –50 to -80°C. Preferably, reagents are added at reduced temperature, such as –30 to -80°C, and then once all reagents are added, the reaction mixture is allowed to warm to 15 to 20°C.

Alternatively, the compound of formula (3) may be obtained directly from a compound of formula (1), for example by treatment with dimethysulphoxide and an acid acceptor.

The coupling of the compound of formula (3) with the compound of formula (4) may employ conditions analogous to those given in WO01/85702 for the corresponding coupling of a compound of formula (4). Alternatively, conditions comprising refluxing the compounds of formula (3) and (4) in a hydrocarbon solvent, such as toluene or cyclohexane, or mixtures thereof, followed by contact with aqueous acid, such as aqueous HCl may be employed.

Alkyl, aryl, alkoxy or aryloxy groups which may be represented by R^7 and R^8 include C_{1-6}alkyl groups, such as methyl and ethyl groups, C_{6-12}aryl groups, such phenyl, tolyl or naphthyl, C_{1-6}alkoy groups, such as ethoxy groups, and C_{6-12}aryloxy groups such as phenoxy groups.

Anions which may be represented by X include halide.

R^6 preferably is $P(=O)R^7R^8$ where R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group.

When W represents OP^2, the protecting group may be removed to form a hydroxy group by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

Oxidation of compounds formed by deprotection of compounds wherein W represents $–OP^2$ may employ conditions known in the art for the oxidation of pyranols to pyranones, and include those given in "Comprehensive Organic Transformations", R.C. Larock, 2nd Ed (1999) p 1670, published by Wiley VCH, incorporated herein by reference. Preferred oxidation systems include Ag_2CO_3/Celite, especially Celite J2, bromine or Swern.

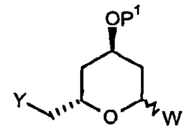
Ring opening of the compounds of formula (5), when W represent =O or formula (6) may employ conditions known in the art for ring opening of a pyranone. Preferably, the ring is opened by contact with a base, such as sodium hydroxide or calcium oxide. Conveniently, polar solvents are employed, for example methanol, acetonitrile, tetrahydrofuran or mixtures thereof.

Remaining protecting groups may be removed by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride,

and benzyl groups may be removed by treatment with TMSI or under selective hydrogenation conditions.

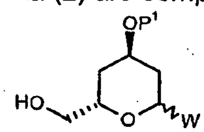
It will also be recognised that compounds of formulae (2), (3) and (5) may also be subjected to oxidation (when W represents –OH) or deprotection and oxidation (when W represents (-O-protecting group) to form the corresponding compound wherein W represents =O.

Preferred compounds of formula (1) are compounds of formula:



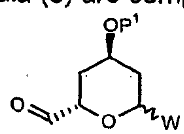
wherein W, P^1 and Y are as previously described.

Preferred compounds of formula (2) are compounds of formula:



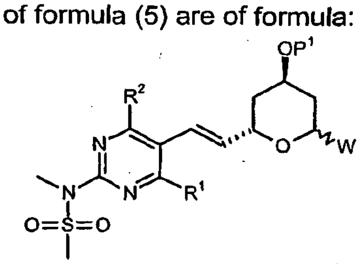
wherein W and P^1 are as previously described.

Preferred compounds of formula (3) are compounds of formula:



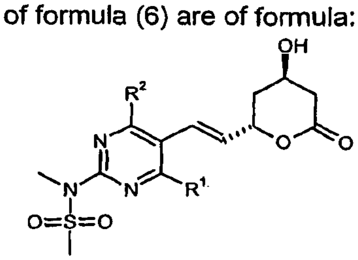
wherein W and P^1 are as previously described.

Preferred compounds of formula (5) are of formula:



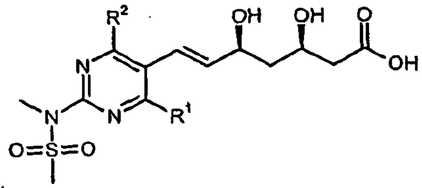
wherein R^1, R^2, W and P^1 are as previously described.

Preferred compounds of formula (6) are of formula:



wherein R^1 and R^2 are as previously described.

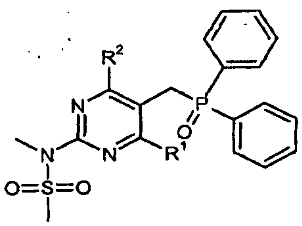
Preferred compounds of formula (7) are of formula:



wherein R^1 and R^2 are as previously described.

Compounds of formula (7) are advantageously converted to pharmaceutically acceptable salts, especially their calcium salts (for example WO01/60804).

Compounds of formula (4) are advantageously prepared by the methods given in WO00/49014 and WO01/85702. Particularly preferred compounds of formula (4) are compounds of formula:



Compounds of formula (1) are advantageously prepared by enzyme catalysed condensation of acetaldehyde and 2-haloacetaldehyde, for example using the method given in US patent 5,795,749.

Compounds of formulae (2) and (3) and, when W is OP^2, formula (5) form further aspects of the present invention.

The invention is illustrated by the following examples.

Example 1 - Preparation of Chlorolactol methyl acetal ((2S,4R)-2-(chloromethyl)-6-methoxytetrahydro-2H-pyran-4-ol), a compound of Formula 1 where Y = Cl, P^1 = H and W = $-OP^2$, in which P^2 = Me.

Crude chlorolactol (15g) was dissolved in methanol (150ml) and heated to 40°C for 2 hours in the presence of 0.1ml sulphuric acid. The solvent was removed by rotary evaporation to afford the product as a dark brown flowing oil. The product was dissolved in DCM and washed with sodium bicarbonate solution. The solvent was removed by rotary evaporation to afford the product as a dark brown flowing oil, which was purified by column chromatography (16.1g) containing a mixture of anomers m/z 179, 149 and 113; ^1H nmr $CDCl_3$ 3.6-3.7 (m 2H), 4.1 (m 1H), 1.5-1.6 (m 2H), 4.0 (m 1H), 1.3-1.6 (m 2H), 4.9 (m 1H), 3.3 & 3.5 (s 3H); ^{13}C nmr $CDCl_3$ 32, 36, 45, 55&56, 64, 65, 94.

Example 2 - Preparation of O-benzyl-chlorolactol methyl acetal ((2S,4R)-4-(benzyloxy)-2-(chloromethyl)-6-methoxytetrahydro-2H-pyran), a compound of Formula 1 where Y = Cl, P^1 = Bn and W = $-OP^2$, in which P^2 = Me.

Chlorolactol methyl acetal (1g) was dissolved in THF (5ml) and charged to sodium hydride (0.33g 60% in mineral oil) in THF (5ml) at room temperature. Benzyl bromide (1.9g) was added dropwise and the mass heated to 80°C for 2 hours. Methanol (2ml) was added and the mass was partitioned between DCM/ water, and was then washed with water. The organic phase was dried and the solvent was removed by rotary evaporation to afford an orange flowing oil (2.1g), containing a mixture of anomers containing a mixture of anomers. m/z 270; 238; 203; 132; 91; ^{1}H nmr $CDCl_3$ 1.6-2.0 (m 4H), 3.4 & 3.5 (s 3H), 3.6 (m 2H), 3.8 (m 1H), 4.0 (m 1H), 4.5 (m 2H), 4.7 (m 1H), 7.3-7.5 (m 5H); ^{13}C nmr $CDCl_3$ 32&33, 46, 55&56, 58, 66, 74, 96&98, 128-131.

Example 3 - Preparation of Hydroxy-O-benzyl-lactol methyl acetal ([(2R,4R)-4-(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl]methanol), a compound of Formula 2 where P^1 = Bn and W = $-OP^2$, in which P^2 = Me.

Preparation of the Acetate Intermediate:

To a 3-litre three necked round bottomed flask flushed with dry nitrogen the O-benzyl-chlorolactol methyl acetal (30g) was charged into dry N-methyl pyrollidinone (756mls). Anhydrous tetrabutylammonium acetate (102.57g) was also charged to the solution. The reaction mixture was then heated at 100°C for 24 hours. The reaction mixture was sampled at routine intervals and directly analysed by tlc and gc/ms.

The black solution was then diluted with water (150mls) and extracted with ethyl acetate (3 x 1500mls). The combined upper organic layer was then washed with water (3 x 1500mls). The aqueous portion showed no product content at this point. The layers were then separated, dried, (Na_2SO_4) and the solvent removed *in vacuo* to yield a black flowing oil (31g, 95%) containing a mixture of anomers. ^{1}H nmr $CDCl_3$ 1.4-1.8 (m 4H), 2.0-2.1 (duplicate s, 3H), 3.4 & 3.5 (s 3H), 3.8 (m 1H), 4.0 (m 1H), 4.1 (m 2H), 4.5 (m, 2H), 4.7-4.9 (m 1H), 7.2-7.3 (m, 5H); ^{13}C nmr $CDCl_3$ 20.8; 30-35; 55&56; 57&64; 66&68; 69&72; 70&71; 98&99; 127-128 & 138; 170.5; m/z 293, 262, 221, 203, 156, 91 and 43.

Preparation of the Alcohol from the Acetate Intermediate:

To a 50mls three necked round bottomed flask flushed with dry nitrogen the O-benzyl-chlorolactol methyl acetal acetate (2g) was charged into dry methanol (10mls) containing anhydrous potassium carbonate (1g). The resultant suspension was stirred at 20°C for 30 minutes. G.C./M.S. showed complete conversion of acetate to alcohol. The solid was filtered off and the solvent removed *in vacuo* to yield a brown flowing oil containing a mixture of anomers (1.6g, 93%). ^{1}H nmr $CDCl_3$ 1.4-1.8 (m 4H), 3.4 & 3.5 (s

3H), 3.8 (m 1H), 3.9 (m 1H), 4.0 (m 2H), 4.5 (m 2H), 4.7-4.9 (m 1H), 7.2-7.3 (m, 5H); ^{13}C nmr $CDCl_3$ 30-38; 55&56; 65&66; 65&69; 70&71; 72&73; 99&100; 128 & 140; m/z 252, 221, 189, 163, 114 and 91.

Example 4 - Preparation of formyl-O-benzyl-lactol methyl acetal (2S,4R)-4-(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-carbaldehyde a compound of Formula 3 where P^1 = Bn and W = –OP^2, in which P^2 = Me.

Dess-Martin periodinane reagent (1.91g) in dichloromethane (50mls) was charged to a 1000 mls round bottomed flask purged with dry nitrogen. The hydroxy-O-benzyl-lactol methyl acetal (1.0g,) was dissolved in dichloromethane (50mls) and added to the Dess-Martin periodinane reagent at 20°C. The reaction mixture was then stirred at room temperature for 30 minutes. The reaction was monitored by tlc. The reaction mixture was then diluted with diethyl ether (500 mls) to precipitate the excess reagent. The suspension was then washed with 10% aqueous sodium hydroxide (200mls). The upper organic layer was then washed with water (250mls). The upper organic layer was then separated, dried (Na_2SO_4) and the solvent removed in vacuo to yield a dark flowing oil as a mixture of anomers (0.8g).

^1H nmr $CDCl_3$ 1.6-1.9 (m 4H), 3.3 & 3.5 (s 3H), 3.7 (m 1H), 3.8 (m 1H), 4.4 (m 2H), 4.7-4.9 (m 1H), 7.2-8.1 (m, 5H), 9.6-9.7 (2 x s, 1H).

^{13}C nmr $CDCl_3$ 30-38; 55&56; 65&66; 65&69; 70&71; 99&100; 128 & 140; 201.

m/z 250, 221, 189, 163, 143, 117 and 91.

Alternatively, a Swern oxidation can be carried out as illustrated by the following example:

A stirred solution of oxalyl chloride (0.037 cm^3, 0.44 mmol) in dichloromethane (4 cm^3) under nitrogen was cooled to –78 C and DMSO was added in one portion. A solution of the alcohol (100 mg, 0.40 mmol) in dichloromethane (1 cm^3) was added to the reaction mixture and the reaction mixture stirred at –78 C for 5 min. Triethylamine (0.272 cm^3, 19.8 mmol) was added and the resulting solution was stirred at –78 C for 25 min and used immediately without isolation or purification. Tlc r_f 0.40 ethyl acetate:hexane (1:1) orange spot with 2,4-dinitrophenylhydrazine stain

Example 5 - Preparation of Pyrimidyl-ethenyl-O-benzyl-lactol methyl acetal, a compound of Formula 5 where R^1= iPr, R^2= 4-FC_6H_4, R^3=Me, R^4=SO_2Me, P^1 = Bz and W = –OP^2, in which P^2 = Me.

Pyrimidyl-ethenyl-O-benzyl-lactol methyl acetal was obtained by first dissolving 0.21g of the compound of formula 4 wherein R^3=Me, R^4=SO_2Me and R^6=PO(Ph)$_2$ in 10ml dry THF, cooling to -60°C and then adding 0.2ml of a 2M solution of sodium hexamethyldisilazide. After 20min, a solution of 0.1g formyl-O-benzyl-lactol methyl acetal in 10ml dry THF at -30°C was added. The reaction mixture was then maintained at this temperature for 8 hours and monitored by tlc. The reaction mixture was allowed to slowly warm up to 20°C. Glacial acetic (5mls) acid was then charged to quench the reaction. Water (5mls) was also charged to the mixture. The solvent was then removed in vacuo and reconstituted with toluene (15mls) and water (15mls). The upper organic layer was then separated and the aqueous layer was then washed with ethyl acetate (15 mls). The combined organics were then dried and the solvent removed in vacuo to yield an oil containing a mixture of isomers, that can be purified by chromatography. The desired product had the tentative NMR assignment

^{1}H nmr $CDCl_3$ 1.2 (d, 6H), 1.6-1.9 (m 4H), 3.3 (s, 3H), 3.4 (s, 3H), 3.2 & 3.5 (2 x s, 3H), 3.7 (m 1H), 3.8 (m 1H), 4.2 (m 1H), 4.4 (m 2H), 4.7-4.9 (m 1H), 5.35 (dd, 1H), 5.85-6.7 (d, 1H), 7.1-8.1 (m, 9H).

Example 6 - Preparation of Pyrimidyl-ethenyl-OH-lactol methyl acetal (Rosuvastatin Lactol-OMe) a compound of Formula 5 where R^1= iPr, R^2= 4-FC_6H_4, R^3=Me, R^4=SO_2Me, P^1 = H and W = –OP^2, in which P^2 = Me.

Pyrimidyl-ethenyl-OH-lactol methyl acetal may be obtained by reaction of Pyrimidyl-ethenyl-O-benzyl-lactol methyl acetal with TMSI.

Example 7 - Preparation of Pyrimidyl-ethenyl-OH-lactol (Rosuvastatin Lactol), a compound of Formula 5 where R^1= iPr, R^2= 4-FC_6H_4, R^3=Me, R^4=SO_2Me, P^1 = H and W = –OP^2, in which P^2 = H

Pyrimidyl-ethenyl-OH-lactol may be obtained by treatment of the Pyrimidyl-ethenyl-OH-lactol methyl acetal with 0.1N HCl in methanol.

Example 8 - Preparation of Lactone, a compound of Formula 6 where R^1= iPr, R^2= 4-FC_6H_4, R^3=Me, R^4=SO_2Me, P^1=H

The pyrimidyl-ethenyl-OH-lactol (35mg, 0.065mmol) in dichloromethane (0.5ml) was added to Dess-Martin periodinane (30mg, 0,07mmol) and stirred at room temperature for 2.5 hours. The reaction was partitioned between 1M sodium hydroxide and diethyl ether. The phases were then separated and the organic volume reduced in vaccuo to afford the crude product oil.

Example 9 - Preparation of Rosuvastatin (hydrolysis of Lactone), a coumpound of Formula 7 where R^1= iPr, R^2= 4-FC_6H_4, R^3=Me, R^4=SO_2Me

The lactone (1.1g) was dissolved in ethanol (10ml). Water (2ml) and $Ca(OH)_2$ (0.15g) were added and the suspension warmed to 60°C for 3 hours. A further 10ml of warm water was added, then the mixture allowed to cool slowly to room temperature. The precipitate formed was filtered and dried to give Rosuvastatin calcium salt. The material was identical to an authentic sample by mixed melting point, NMR and mass spectrometry.